Timing of Brain Metastases Development in Metastatic Renal Cell Cancer patients treated with Targeted Therapies and Survival Outcomes: an Australian Multicentre Study

Running title: Impact of brain metastases in renal cell carcinoma

Francis J. Ha¹ MBBS BMedSc and Lavinia Spain¹ MBBS BMedSc FRACP*, Anthony Dowling² MBBS FRACP, Edmond M. Kwan³ MBBS FRACP, Carmel Pezaro⁴ MBBS DMedSc FRACP, Daphne Day⁵ MBBS FRACP, Puey Ling Chia¹ MBBS MRCP FRACP, Ben Tran⁵ MBBS FRACP,*

David Pook³ BMedSc MBBS MD FRACP, Andrew J. Weickhardt¹ MBBS DMedSc FRACP

*Both authors contributed equally to this manuscript

¹Olivia Newton-John Cancer Research Institute, Austin Hospital, Melbourne, Australia

²Department of Medical Oncology, St Vincent's Hospital, Melbourne, Australia

³Department of Medical Oncology, Monash Health, Melbourne, Australia

⁴Eastern Health and Monash University, Melbourne, Australia

⁵Peter MacCallum Cancer Centre, Melbourne, Australia

Correspondence:

A/Prof Andrew Weickhardt

Medical Oncologist

Email: andrew.weickhardt@onjcri.org.au

Phone: +61 3 9496 5726

Olivia Newton-John Cancer Research Institute, Austin Hospital

145 Studley Road, Heidelberg, Victoria 3084

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ABSTRACT

Aim

Targeted therapy (TT) has improved survival for metastatic renal cell carcinoma (mRCC). However survival is usually limited if brain metastases (BM) develop. We aimed to evaluate survival outcomes in mRCC patients based on timing of BM diagnosis.

Methods

We conducted a multi-centre, retrospective study of mRCC patients with BM who received TT at any point between 2005-2014. We determined overall survival (OS) from stage IV diagnosis, TT initiation and BM diagnosis, and prognostic factors. Patients were grouped into 3 categories: synchronous-BM, metachronous-BM diagnosed while conservatively-managed (metachronous-BM before TT) and metachronous-BM diagnosed during TT. Survival was calculated by Kaplan-Meier method and predictors calculated using Cox-hazards-regression.

Results

Incidence of BM was 17% in mRCC patients treated with TT (2 centres). Fifty-four mRCC-BM patients were identified from 5 tertiary centres. 28% (15/54) had synchronous-BM, 28% (15/54) had metachronous-BM before TT, and 44% (24/54) had metachronous-BM during TT. Most had CNS symptoms at BM diagnosis (78%; 42/54). Median OS from stage IV diagnosis, TT commencement and BM diagnosis was 28 months (95%CI 16-43), 19 months (95%CI 9-26) and 9 months (95%CI 5-16), respectively. Synchronous-BM group trended towards poorer survival from TT commencement ($p=0.06$). Metachronous-BM during TT group had lower survival from BM diagnosis than synchronous-BM and metachronous-BM before TT group ($p<0.001$). Eight of 50 deaths (16%) were from neurological complications. Presence of CNS symptoms did not predict worse survival from stage IV diagnosis ($p=0.73$).

Conclusion

In patients with mRCC, the development of BM whilst on TT portends shorter prognosis compared with synchronous diagnosis of BM at Stage IV disease or metachronous BM developed prior to commencing TT. The presence of CNS symptoms does not predict worse survival.

Keywords: targeted therapy, brain metastasis, renal cell carcinoma, survival, prognosis

INTRODUCTION

Targeted therapies (TT) such as vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors prolong survival in patients with mRCC.[1, 2] However, in patients who develop brain metastases (BM), survival is diminished and quality of life may be compromised by progressive neurological deficits.[3]

Brain metastases develop in 10-15% of patients with metastatic renal cell carcinoma (mRCC).[4-6] Prior studies have reported an overall survival of between 10-14 months in patients with mRCC and brain metastasis.[4-7] Independent predictors of poorer overall survival include the Karnofsky performance score (KPS) <80%, diagnosis to treatment with targeted therapy time of <1 year, increased number of brain metastases,[5] age and histology sub-type.[8, 9]

The utility of screening for BM in mRCC is unknown and clinical practice varies.[10, 11] International guidelines do not currently recommend routine screening for asymptomatic mRCC-BM.[12, 13] While a recent study reported that there was no difference in overall survival from BM diagnosis between mRCC patients with synchronous or metachronous BM, there was no further breakdown in the timing of metachronous BM diagnosis in relation to TT commencement, and whether patients had symptomatic central nervous system (CNS)

disease at diagnosis.[14] A further understanding of the timing and presentation of mRCC-BM could provide insight into the evolution of disease.

Our study aimed to describe the timing and presentation of BM in patients with mRCC, and investigate the prognostic factors including the impact of synchronous versus metachronous diagnosis of BM.

METHODS

We conducted a multi-centre, retrospective, medical record review study. Ethics approval from the relevant institutional review boards of the 5 tertiary centres was obtained. Patients were identified through systematic review of pharmacy records or from a pre-existing database (1 centre). We included patients aged ≥ 18 years who had a diagnosis of mRCC and BM between 1 January 2005 and 31 December 2014. Included patients must have received TT for mRCC, either before, during or after their diagnosis of BM. To determine the incidence of BM, data were obtained from two out of the five included centres for mRCC patients with or without BM treated with TT during the study period.

We collected data in relation to baseline demographics and mRCC diagnosis, including the date of mRCC diagnosis, baseline physical function as measured by the Eastern Cooperative Oncology Group Score (ECOG),[15] and clinical/pathologic data to determine baseline prognosis according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score based on anaemia, thrombocytosis, neutrophilia, Karnofsky performance status [KPS] <80 , <1 year from diagnosis to first-line targeted therapy, hypercalcaemia.[16] Type, timing and duration of targeted therapy was also collected, whereby types were defined as anti-vascular endothelial growth factor tyrosine kinase inhibitors (TKI) including sunitinib, pazopanib and sorafenib, or mTOR inhibitors (mTORI) including everolimus and temsirolimus. In relation to BM diagnosis, extracted data included

date of BM diagnosis, central nervous system (CNS) symptoms at presentation and treatment received. Brain metastases diagnosed within 2 months of detection of metastatic disease were considered as synchronous BM, as opposed to those diagnosed more than 2 months later, which were considered metachronous. For survival outcomes, data were collected on the timing of death as well as cause of death, which was attributed to either a central neurological event – all presumed cancer-related, a non-neurological but cancer-related event (including treatment toxicity), or other/unknown cause.

Statistical analysis

In mRCC-BM patients, groups were stratified *a priori* according to timing of BM diagnosis, being either synchronous or metachronous in relation to systemic disease diagnosis. Patients with synchronous BM did not necessarily received TT at the time of diagnosis and treatment decisions were at the discretion of the treating clinician. For patients with metachronous disease, patients were further stratified according to BM development in relation to targeted therapy, being either prior to commencement of targeted therapy (e.g. initial observation for systemic disease) or during treatment.

Comparisons between groups for baseline demographics, treatments received and causes of death were performed using Pearson's chi-square test for categorical data and Analysis of Variance for continuous data. Categorical data are presented as numerical counts with percentages and continuous data are presented as a median with interquartile range (IQR) or as mean with range where data were not normally-distributed. Overall survival (OS) was calculated from time of initial stage IV diagnosis, time of TT commencement and time of BM diagnosis until time of last available contact (dead or alive). We used the Kaplan-Meier method to determine OS which is presented as a median with 95% confidence interval (CI). Where applicable, log rank test was used to compare dichotomous variables. To evaluate clinically relevant predictors of OS, univariable analysis was performed using Cox hazards

regression model. P-value of <0.05 was considered statistically significant. Variables that were significant in the univariable model were included in multivariable analysis. Statistical analyses were performed using Stata MP 14.0 (Stata Corp LP, College Station, TX).

RESULTS

For two out of the five centres included in our study, a total of 196 mRCC patients who had received TT, with or without BM, were identified through pharmacy record review. In this group, 8 patients had BM present at time of initial stage IV diagnosis while a further 26 patients developed BM over a median follow-up of 36 months, forming an overall BM incidence of 17% (34/196).

Across the five centres, we identified 54 patients who met the pre-specified inclusion criteria with metastatic RCC and BM. The median age was 59 years (IQR, 49-64) and most were male (81%). Clear cell histology was the most common subtype (80%) and 43% (23/54) had stage IV disease at the time of initial RCC diagnosis with most of these including the presence of BM (15/23). Most patients had a prior nephrectomy (80%; 43/54) with 30% (13/43) occurring in the setting of known metastatic disease (**Table 1**).

In relation to the timing of BM diagnosis, 15 patients (28%) had synchronous BM (i.e. diagnosed <2 months from stage IV diagnosis) although TT commencement occurred a median of 6 months (IQR 2.1-26 months) after stage IV diagnosis. In patients with metachronous BM, 15 patients developed BM prior to the commencement of any targeted therapy with a median time from stage IV diagnosis to BM diagnosis of 8.6 months (IQR, 5.5-36 months). A further 24 patients with metachronous BM were diagnosed with BM after commencement of TT. In this group (i.e. metachronous BM during TT), the median time from stage IV disease to commencement of TT was 2.3 months (IQR, 1.2-4.9 months) and

the median time from TT commencement to BM diagnosis was 12.2 months (IQR, 5.0-30 months).

In relation to TT exposure, most patients received a TKI during their disease course (52/54; 96%), while 28% (15/54) had received an mTOR inhibitor at some stage (**Table 1**). For patients with metachronous BM developed during TT, most were on a TKI prior to BM diagnosis (19/24). Similarly most continued on a TKI after BM diagnosis (18/24) with only 3 patient ceasing systemic therapy. For CNS treatment, patients commonly received whole brain radiation therapy (39/54; 72%) and/or neurosurgery (31/54; 57%). Fewer patients received stereotactic body radiation therapy or stereotactic radiosurgery (11/54; 20%), however patients with metachronous BM developed while on TT were less likely to receive these localized CNS radiotherapy treatments ($p=0.01$; **Table 1**).

In mRCC patients with or without BM identified from 2 centres, there was no significant difference in OS from stage IV diagnosis between those with or without BM (median OS 24.9 months [IQR 8.4-47 months] versus 23.8 months [IQR 9.8-50 months], respectively; log-rank for difference, $p=0.17$). In mRCC patients with BM from across the 5 centres, fifty patients had died (93%) after a median follow-up of 25.9 months (IQR 9.6-50.2 months) from stage IV diagnosis to last known contact. The median OS from stage IV diagnosis was 27.6 months (95% CI 15.6-42.6 months; **Table 2** and **Figure 1**). Significant univariable predictors of OS from stage IV diagnosis were age of 65 years or more ($p=0.03$), ECOG ($p=0.001$) and nephrectomy (<0.001). Patients with metachronous BM observed prior to TT had a numerically better survival compared with synchronous BM patients but this did not reach statistical significance ($p=0.064$). The IMDC score was not included in these analyses due to missing patient data. Nephrectomy ($p=0.021$) and ECOG status (0.001) remained significant predictors on multivariable analysis (**Table 3**).

The median OS from commencement of TT was 18.5 months (95% CI 8.9-25.7 months) with synchronous BM patients having numerically shorter survival compared with metachronous BM before or during TT ($p=0.06$; **Figure 1**). The median OS from time of BM diagnosis was 8.6 months (95% CI, 5.3-15.6). Patients with synchronous BM having similar survival to patients with metachronous BM prior to TT and numerically higher than patients with metachronous BM developed on while on TT (**Figure 1**).

The most common cause of death was cancer-related without neurological complications (33/50; 66%). Neurological complications secondary to CNS disease accounted for 16% (8/50) of deaths. Of these deaths, 5 patients (83%) had received WBRT and 5 patients underwent neurosurgery (83%), but only 2 patients (25%) underwent SBRT/SRS. Further breakdown of cause of death according to BM presentation is provided in **Table 4**.

DISCUSSION

Main findings

This study evaluated patterns of BM presentation in relation to TT commencement and corresponding survival outcomes in mRCC patients. Consistent with other studies, the incidence of brain metastases was 17%[4-6]. Slightly more than half the patients with mRCC in the overall cohort developed BM prior to commencing TT (28% synchronous and 28% metachronous prior to targeted therapy), with more than three-quarters of these being symptomatic presentations. Patients with synchronous BM had numerically lower survival from stage IV diagnosis and commencement of TT compared with both groups of metachronous BM patients. However patients that developed BM while on TT for systemic disease had significantly worse survival from the time of diagnosis of BM compared with patients whose BM were identified prior to starting TT. The presence of CNS symptoms at time of BM diagnosis did not confer worse survival.

Survival outcomes

The overall survival from initiation of TT in our cohort of mRCC-BM patients (18.5 months) is consistent with findings from the International Metastatic Renal Cell Carcinoma Database Consortium (14.4 months) [5]. While numerically higher, the significant overlap in confidence intervals and greater proportion of patients with synchronous BM (44%) in their study partly accounts for this difference. Similarly, our study confirms the poor prognosis of patients who develop BM while on TT (~5 months survival from BM diagnosis) compared with metachronous BM patients who develop BM during conservative observation. Such findings likely reflect a lower burden of metastatic disease in patients who undergo initial close observation rather than commencing TT,[17] in contrast to patients already on TT who may have more bulky visceral sites of systemic disease. Thus the development of BM during TT for systemic disease is suggestive of generalized disease progression, especially given that none of these patients are deemed to have died from neurological complications but rather other cancer-related issues.

Role of screening for brain metastases

The utility of screening for BM in mRCC patients remains to be demonstrated from our study. Most of the included patients were symptomatic at presentation, yet the presence of CNS symptoms was not associated with poorer survival. This is consistent with previous data[8] and could suggest that patients with early symptomatic CNS disease are more amenable to CNS treatment and thus the presence of symptoms alone may not necessarily confer a poorer prognosis. Screening behaviours of Australian oncologists currently vary - an online, ethics-approved survey of genito-urinary medical oncologists reported that 28% (5/18) perform routine CNS imaging.[18] Our data show that the median time to the development of BM in conservatively managed patients was 8.6 months while in those who

had already commenced TT, the median time was 14.5 months from initial stage IV diagnosis. It remains uncertain at what timeframe screening should be undertaken given the large associated interquartile ranges and at what time intervals patients should be potentially re-screened. Another aspect when considering screening is determining the most sensitive but cost-effective imaging modality to use. While magnetic resonance imaging is superior in detecting BM compared with computed tomography,[19] which is important given the growing use of SBRT to treat smaller lesions, there are obvious cost and access limitations to using this modality. Further data that encompasses mortality, morbidity, quality of life and cost associated with earlier identification of CNS disease in prospective data are needed to determine the benefit of routine CNS screening.

Clinical implications

There are currently sparse data evaluating outcomes of mRCC patients with brain metastases in Australia, particularly given their typical exclusion from clinical trials in the targeted therapy era. This multi-centre descriptive observational study provides further insight into treatment outcomes and expected survival for this unique patient cohort. This information may aid clinicians when discussing prognosis with patients or inform treatment decisions influenced by life expectancy[20]. Survival outcomes are consistent with international data and similarly confirms our treatment practices[5, 6]. While synchronous BM portends poor prognosis overall, the development of BM on systemic therapy also confers limited survival unrelated to CNS disease itself but rather as a marker of generalized disease progression. Finally, we find that symptomatic CNS disease does not confer worse survival compared with asymptomatic presentation, and the routine use of CNS screening cannot be supported until further prospective data can clarify its survival and economic benefit.

Limitations

There are some limitations when considering the findings from this study. First, inconsistent reporting of data in a small cohort may limit interpretation, particularly regarding independent predictors of OS where certain predictors such as IMDC score could not be included due to insufficient data. Additionally, we did not have access to data regarding number and size of CNS lesions which have been identified as potential prognostic factors,[5, 14] nor other sites of metastases to indicate disease stability when considering CNS treatment. Second, no patients included in our study were exposed to immune checkpoint inhibitors, which impact survival and may alter the timing and development of CNS metastases. Third, these data only capture patients who received TT and thus outcomes are skewed towards being more favourable compared with patients who were managed with best supportive care following BM diagnosis, particularly in the synchronous BM and metachronous BM observed prior to TT groups. Fourth, knowledge of new metastases that may have been diagnosed concurrent to BM could impact both prognosis and treatment decisions. While this information was not collected in these data, mRCC prognosis may be influenced by extracerebral metastases more so than BM and this is supported by the lack of survival difference between mRCC patients with or without BM identified from 2 out of the 5 centres[6]. Lastly, there was no consistent approach to CNS imaging in the absence of symptoms between the included institutions. Without baseline imaging, it remains uncertain whether some patients had very small asymptomatic BM even from their initial RCC diagnosis.

CONCLUSION

In patients with mRCC, the development of BM whilst on TT portends shorter prognosis compared with synchronous diagnosis of BM at Stage IV disease or metachronous BM developed prior to commencing TT. The presence of CNS symptoms does not confer worse survival and argues against routine CNS screening although prospective randomized data are needed to address this clinical dilemma.

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FIGURE LEGEND

Figure 1. Overall survival from (A) stage IV diagnosis (B) targeted therapy commencement and (C) BM diagnosis.

BM, Brain metastasis; Metach, Metachronous; Synch, Synchronous; TT, Targeted therapy

Table 1. Patient baseline characteristics

Baseline characteristics	Total (n=54)	Synch-BM (n=15)	Metach-BM: observed prior to TT (n=15)	Metach-BM: developed during TT (n=24)	p-value for difference
Age, median years (IQR)	59 (49-64)	57 (45-68)	61 (55-64)	57 (49-63)	0.80
Female (%)	10 (19)	1 (7)	2 (13)	7 (29)	0.18
Stage IV disease at initial diagnosis (%)	23 (43)	7 (47%)	3 (20)	13 (54)	0.10
Prior nephrectomy (%)	43 (80)	9 (60)	13 (87)	21 (88)	0.09
Histology (%)					
Clear cell	43 (80)	13 (87)	12 (80)	18 (75)	0.35
Non-clear cell	9 (17)	1 (7)	2 (13)	6 (25)	
Not documented	2 (4)	1 (7)	1 (7)	0	
ECOG at BM diagnosis (%)					
0-1	28 (52)	8 (53)	9 (60)	11 (46)	0.21
≥2	13 (24)	4 (27)	1 (7)	8 (33)	
Not documented	13 (24)	3 (20)	5 (33)	5 (21)	
Baseline IMDC score risk (%)					
Favourable	2 (4)	0	1 (7)	1 (4)	0.19
Intermediate	19 (35)	7 (47)	7 (47)	5 (21)	

Poor	5 (9)	1 (7)	0	4 (17)	
Not documented	28 (52)	7 (47)	7 (47)	14 (58)	
CNS symptoms at BM diagnosis (%)					
Yes	42 (78)	14 (93)	10 (67)	18 (75)	0.10
No	10 (19)	0	4 (27)	6 (25)	
Not documented	2 (4)	1 (7)	1 (7)	0	
Any targeted therapy exposure (%)					
TKI	52 (96)	15 (100)	14 (93)	23 (96)	0.62
mTOR inhibitor	15 (28)	2 (13)	3 (20)	10 (2)	0.12
CNS treatment (%)	52 (97)	14 (93)	15 (100)	23 (96)	0.62
WBRT	39 (72)	9 (60)	10 (67)	20 (83)	0.24
Neurosurgery	31 (57)	12 (80)	8 (53)	11 (46)	0.10
SBRT or SRS	11 (20)	4 (27)	6 (40)	1 (4)	0.01

BM, Brain metastasis; CNS, Central nervous system; ECOG, Eastern Cooperative Group Score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, Interquartile range; Metach-BM, Metachronous brain metastasis; Synch-BM, Synchronous brain metastasis; TT, Targeted therapy

Table 2. Overall survival

	Overall	Synchronous BM	Metach-BM prior to TT	Metach-BM during TT	p-value for difference
OS from Stage IV	27.6 (15.6-42.6)	15.6 (5.1-32.0)	54.2 (18.2-80.1)	27.6 (10.8-44.0)	0.17
OS from TT commencement	18.5 (8.9-25.7)	5.1 (2.2-18.5)	19.6 (5.5-40.0)	22.8 (8.9-36.8)	0.06
OS from BM diagnosis	8.6 (5.3-15.6)	15.6 (3.7-31.8)	18.1 (6.7-33.9)	5.1 (2.4-7.7)	0.0002

Data are presented in median months (95% confidence interval)

BM, Brain metastases; Metach, Metachronous; OS, Overall survival; TT, Targeted therapy

Table 3. Predictors of overall survival from stage IV diagnosis

Predictors	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, ≥ 65 years	2.48 (1.10-5.58)	0.028	0.66 (0.21-2.03)	0.46
Male	1.86 (0.75-4.61)	0.18		
ECOG	2.87 (1.58-5.20)	0.001	3.39 (1.60-7.20)	0.001
Histology, clear-cell	0.58 (0.27-1.20)	0.14		
Nephrectomy	0.15 (0.06-0.33)	<0.001	0.32 (0.12-0.84)	0.021
Timing of BM and TT				
Synchronous BM	1 (reference)			
Metachronous BM – observation prior to TT	0.47 (0.21-1.05)	0.064		
Metachronous BM – developed while on TT	0.66 (0.33-1.34)	0.25		
CNS symptoms at BM diagnosis	1.15 (0.51-2.62)	0.73		

BM, Brain metastasis; CI, Confidence interval; CNS, Central nervous system; ECOG, Eastern Cooperative Group Score; HR, Hazard ratio; Metach-BM, Metachronous brain metastasis; Synch-BM, Synchronous brain metastasis; TT, Targeted therapy

Table 4. Cause of death

Cause of death (%)	Total (n=50)	Synch-BM (n=13)	Metach-BM: observed prior to TT (n=12)	Metach-BM: developed during TT (n=21)
Neurological complication	8 (16)	5 (36)	3 (25)	0
Cancer-related cause	33 (66)	8 (57)	6 (50)	19 (90)
Other/Unknown	9 (18)	0	3 (25)	2 (9)

BM, Brain metastasis; Metach-BM, Metachronous brain metastasis; Synch-BM, Synchronous brain metastasis; TT, Targeted therapy

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Author/s:

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